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(21) International Application Number: PCT/NO99/00346 (22) International Filing Date: 16 November 1999 (16.11.99) (30) Priority Data: 19990975 1 March 1999 (01.03.99) NO (71) Applicant (for all designated States except US): ORIX AS [NO/NO]; Caroline Overlands Vei 12a, N-1356 Bekkestua (NO). (72) Inventor; and (75) Inventor/Applicant (for US only): RÖLLA, Gunnar [NO/NO]; Bygdøy Allé 56a, N-0265 Oslo (NO). (74) Agent: GÖRBITZ, Johan, H.; Bryn & Aarflot AS, P.O. Box 449 Sentrum, N-0104 Oslo (NO).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, HE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: ORAL COMPOSITION FOR INHIBITING ORAL MALODOR		
(57) Abstract		
<p>Oral composition for inhibiting oral malodor, containing an antibacterial agent and a zinc compound, in the form of a mouthwash containing 0.005–0.05 % w/v of an antibacterial agent selected from bis-guanides and quaternary ammonium compounds, and 0.05–0.5 % w/v of zinc acetate.</p>		

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Oral composition for inhibiting oral malodor.

The present invention relates to an oral composition which is effective against halitosis (oral malodor, foetor ex ore). Said composition is effective by eliminating or reducing the production of volatile sulfur compounds (VSCs) in the oral cavity. It is well established that in the majority of cases of halitosis this originates from the oral cavity and not from the stomach, as frequently believed by the public.

Bacteria located in the crypts at the back of the tongue and in periodontal pockets produce VSCs, mainly hydrogen sulfide (HS) and methyl mercaptan (MM). The bacteria produce these by proteolytic, anaerobic metabolism, and they have an extremely unpleasant odor even in very low concentrations. The VSCs are able to penetrate epithelium and have pathogenic potentials by damaging cells of the underlying tissues and also affect their metabolism. It has been suggested that the VSCs produced by bacteria in periodontal pockets may well be an important factor in the development of periodontal disease. MM appears to have a higher pathogenic potential than HS and has also a more offensive odor.

The most important substrate for HS production in the oral cavity appears to be cysteine. HS forms immediately upon rinsing the mouth with an aqueous solution of this amino acid (see example 2). Methionine is a major substrate for MM formation, although this compound is not as rapidly formed in the oral cavity as hydrogen sulfide.

It is known that zinc ions reduce the VSC production in the oral cavity. The mechanism involved presumably involves a reaction between zinc and sulfur whereby non-volatile sulfides are formed and thus inhibit the transformation of sulfur containing substrates to VSCs. Zinc furthermore possesses a certain antibacterial activity and this metal ion is known to be able to inhibit plaque formation and reduce acid formation in dental plaque. The zinc salts usually used for such purposes are the chloride, the sulfate and the citrate. However, aqueous solutions of the two former salts have low pH and are thus not necessarily suited for oral use whereas solutions of zinc citrate contain complexes of zinc and citrate and very few free zinc ions.

The problem of getting zinc in a suitable form is the issue of US patent No. 4,289,753 and UK Patent Application No. 2,052,978. In the former the zinc compound used is an ammonium or alkali metal citrate. It is also stated in this patent that this zinc compound may be used in combination with antibacterial agents such as cetyl pyridinium chloride.

The above UK Patent Application discloses an oral composition in which the pH of a zinc-containing solution is adjusted to 4.5 or 8 by means of glycine. The zinc is generally present as zinc chloride.

Antibacterial agents such as cationic bis-biguanides and quaternary ammonium compounds, have been widely used in preventive dentistry as inhibitors of plaque formation and of development of gingivitis. The bis-biguanide chlorhexidine is frequently used for this purpose, usually as an aqueous solution of 0.2% of its gluconate salt, and is applied as a mouthrinse twice daily. Such concentration and frequency are necessary to obtain consistent clinical plaque inhibition. However, chlorhexidine in these concentrations has a bitter taste and causes dental stain. Chlorhexidine forms salts of low solubility with chloride, sulfate and citrate and is thus not compatible with zinc containing these anions.

The other cationic antibacterial agents which inhibit plaque formation, for example cetylpyridinium chloride or benzalkonium chloride, have less clinical effect, but show a less pronounced tendency to cause dental stain. The cationic antibacterial agents mentioned above are able to inhibit VSC formation in the oral cavity, but relatively high concentrations are needed (see Example 1).

It has now unexpectedly been found that anti-VSC effect of zinc ions is mainly directed against hydrogen sulfide production and to a far lesser extent against the production of methyl mercaptan (see Example 1, Fig. 2). The VSC species with highest pathogenic potential and the most unpleasant odor i.e. MM, is thus incompletely eliminated by zinc ions.

This selective effect on HS by zinc can presumably be explained by the fact that cysteine (which is major substrate for HS formation) has an exposed -SH group, which will react readily with zinc ions, whereas methionine (which is a substrate for MM formation) has no such group. When hydrogen sulfide is dissolved in water (or saliva) HS- and S-- are formed (together with two protons), and both these sulfur containing intermediates react rapidly with zinc ions to form insoluble sulfides.

It was furthermore unexpectedly found that when a combination of zinc ions and very low concentrations of certain cationic antibacterial agents were used, the combinations inhibited both HS and MM formation. The effect of the combinations is synergistic (Example 1, table 1). The combinations of zinc and low concentrations of antibacterial agent caused a much higher inhibition of VSCs than any of the individual agents alone. The concentration of an antibacterial agent used in this way against oral malodor was markedly lower than the concentrations needed to obtain plaque inhibition or reduced acid formation in plaque (1/10 or less).

The importance of this invention resides in the fact that it allows the use of very low concentrations of antibacterial agents, i.e. concentrations where their undesired side effects are avoided. The contribution of the antibacterial agent is probably mainly to inhibit MM formation, but synergistic effect with zinc against HS was also observed, although not to the same degree as against MM. The concentration of zinc can also be kept lower than when zinc is used alone, for the same reason. Zinc has a metallic taste which is concentration dependent.

The use of combinations of zinc acetate and chlorhexidine is described in DE 30001575 A1. However, the purpose is to avoid discoloration of teeth by chlorhexidine. In US patent No. 4,522,806 an anti-plaque effect of the combination of chlorhexidine and zinc acetate is mentioned (page 5, first paragraph). The combination was found to be numerically better than chlorhexidine alone, but the difference was not statistically significant.

In US patent 5,906,811 a combination of zinc acetate and benzalkoniumchloride is mentioned as an ingredient in tooth-pastes. The main purpose is to avoid damage from free radical species on the oropharyngeal cavity of tobacco smokers, including secondary smokers.

The present invention provides an oral composition for inhibiting oral malodor, comprising an antibacterial agent and a zinc compound. The composition is in the form of a mouthwash containing 0.005 – 0.05% w/v of an antibacterial agent selected from bis-biguanides and quaternary ammonium compounds, and 0.05 - 0.5 % w/v zinc acetate.

When zinc acetate is used together with an antibacterial agent selected from the bis-biguanides or quaternary ammonium compounds, the effect appears to be synergistic, as mentioned above. This means that by using such a

combination, the amount of both (i.e. zinc acetate and anti-bacterial agent) may be kept very low. By using such low amounts the bitterness of the taste and the tendency to cause dental stain will both be avoided.

5 A major benefit of this invention is that it allows the use of much lower concentrations of antibacterials in compositions specially designed to inhibit oral malodor, than in ordinary products intended for anti-plaque and anti-gingivitis purposes.

The low concentrations of the antibacterial agent is favorable both from an economical and toxicological point of view. The presence of zinc in itself
10 reduces the tendency to cause dental stain, because zinc sulfide is white or gray, whereas the other metal sulfides which form on teeth are black, brown or yellow.

As mentioned above it is a great advantage that the concentrations of the two ingredients, in particular the concentration of the antibacterial agent, can be
15 kept very low. This is particularly easy to control in a mouthrinse where the concentrations of said active ingredients can be readily adjusted to the desired value. According to a particularly preferred embodiment the oral composition of the invention is in the form of a mouthrinse containing from 0.01% to 0.025% w/v of the antibacterials and 0.1% to 0.3% w/v of zinc acetate.

20 As mentioned above, a preferred antibacterial agent is chlorhexidine or a salt thereof, in particular the acetate or the gluconate salts. Preferred quaternary ammonium compounds are cetyl pyridinium chloride or benzalkonium chloride.

According to another embodiment of the invention a composition comprising an antibacterial agent selected from the bis-biguanides and the
25 quaternary ammonium compounds, and zinc acetate, is used for the preparation of an oral composition in particular in a mouthrinse, for inhibiting oral malodor.

In a further embodiment of the invention a composition containing an antibacterial agent selected from bis-biguanides and quaternary ammonium compounds, and zinc acetate, is used for the treatment of oral malodor. In the
30 use indicated above, the amounts of the components should be as described above in connection with the oral composition.

Example 1

In vitro experiments were performed to test the VSC-inhibiting potential of different combinations of zinc acetate and cationic antibacterial agents.

5 To a 1 ml sample of freshly collected human saliva in a test tube was added 10 microliter of the solutions (mouthrinses) described below. The test tubes were closed with a stopper and incubated overnight at 37°C. A control tube which contained only saliva served as a control. It is well known that large amounts of VSCs are formed in a test tube during the latter conditions, the
10 bacteria breaking down the salivary proteins and forming VSCs from cysteine and methionine. The VSCs in the gas phase above the incubated saliva, were measured by gas chromatography in a Shimadzu 14B instrument, and hydrogen sulfide, methyl mercaptan and di-methyl sulfide were used as standard.

The solutions to be tested were: 0,3% zinc acetate, 0.025%
15 chlorhexidine, 0.025% cetylpyridinium chloride and 0.025% benzalkonium chlorides. Subsequently the zinc acetate was combined with each of the individual antibacterial agents. All the experiments described in this paragraph were performed on the same day under identical conditions. The concentrations chosen were based on experience from pilot experiments with different
20 concentrations of the zinc and antibacterial agents. The results can be seen from the chromatograms in figures 1-8, and from table 1 below.

The experiments showed that the control contained very high amounts of both hydrogen sulfide (HS) and methyl mercaptan (MM), whereas the samples which contained zinc had low amounts of both HS and MM. It was, however,
25 found that the zinc acetate reduced the amount of HS much more than the amount of MM. This effect was seen in many experiments with saliva from different subjects.

Addition of chlorhexidine had a clear effect on both HS and MM in the same order of magnitude as zinc acetate. The other antibacterials were
30 effective, but much less so than chlorhexidine or zinc. However, when combinations of zinc acetate and the different antibacterials were tested, a clear further reduction in VSCs was observed, both for HS and MM. It can be seen that chlorhexidine was not better than the other antibacterials in these experiments.

An examination was conducted to investigate whether the effect of the combinations of zinc acetate and the individual antibacterial agents represented a synergistic effect. This was performed according to the method of Behrenbaum (J. Inf. Dis. 137:122-130, 1978). The fractional inhibitory concentrations (the FIC index) was calculated based on the amounts (AUC) of hydrogen sulfide and methyl mercaptan formed under different conditions. A low AUC thus indicates presence of a strong inhibitor. The FIC index was calculated from the following formula: $(A+B)/A + (A+B)/B$, where A+B represents the combinations of zinc and antibacterial agent, whereas A and B alone represent the individual agents.

If the FIC index is below 1 (<1) a synergistic effect is established. If the index is like 1 ($=1$) an additional effect between A and B is seen, whereas an index above 1 (>1) indicates an antagonistic effect. The FIC index of the different combinations is seen in Table 1. All the different combinations had synergistic effect against both HS and MM, but the effect was far stronger against MM, presumably because zinc acetate had a weaker effect against MM (table 1).

Table 1

The table contains the AUC values (amounts of VSCs) from fig. 1-8 and the FIC index* for the combinations of zinc and the individual antibacterial agents.

Fig.	Agents tested	HS	FIC index	MM	FIC index
1	Control	>27 mill		>41 mill	
2	Zinc Ac. 0,3%	150 000		4 mill	
3	CHX 0.025%	443 000		355 000	
4	CPC 0.025%	5.2 mill		6.89 mill	
5	Benzalk 0.025%	1.4 mill		1.7 mill	
6	Zinc Ac 0.3%+CHX 0.025%	82 000	0.73	34 000	0.1
7	Zinc Ac 0.3%+Benzalk. 0.025%	47 000	0.33	13 000	0.01
8	Zinc Ac 0.3%+CPC 0.025%	37 000	0.24	1 000	0.00

AUC - area under curve

Ac - acetate

CHX - chlorhexidine acetate

Benzalk. - benzalkonium chloride

5 CPC; cetylpyridinium chloride

*A FIC index below 1 (<1) indicates a synergistic effect

HS - hydrogen sulfide

MM - methylmercaptane

10 Example 2

It has been shown that aqueous mouthrinses with 6 mM cysteine give an immediate, steep rise in VSC formation in the oral cavity. The effect can be used as a test system by observing the effect of a cysteine rinse when a prerinse with
15 an inhibitor of oral VSC formation is performed (for instance with zinc solutions). This system is described in US patent No. 5.833.955 of Kleinberg et al. (1998). By subsequent cysteine rinses each hour after for instance a zinc solution, it can be shown how long the inhibitor is effective. In the following it was shown that with 0.3% of zinc acetate and 0.025% of each of the antibacterial agents
20 chlorhexidine and cetylpyridinium chloride was effective for more than 5 hours. The experimental design described is presumably severe, and it seems likely that under "normal" conditions where no cysteine is introduced in the mouth, the duration of the effect would be expected to last considerably longer than the present results indicate. A limitation of the model is that only hydrogen sulfide is
25 formed by the test subjects upon cysteine rinses. This is clearly shown when the mouth air is analyzed by gas chromatography, as in the present study. If the frequently used Halimeter is employed for measurement, this limitation is not obvious because the Halimeter operates by chemical sensors which cannot differentiate between hydrogen sulfide and methyl mercaptan. The present
30 experiments thus show the inhibiting effect of the inhibitors on hydrogen sulfide only. However, in combination with the experiments in Example 1 (which examined the effect of the combinations on methyl mercaptan as well) the present experiments are judged to provide valid data.

In the present experiments the test subject rinsed with 5 ml of a 6 mM cysteine solution and the VSC in the mouth air was examined after the mouth had been kept closed for 90 sec. The subject then rinsed with a VSC inhibitor (i.e. combinations of zinc acetate and the respective antibacterial agents). After one hour the subject again rinsed with cysteine. Any reduction in VSC (i.e. hydrogen sulfide) from the original values was assumed to be caused by the inhibitor. Cysteine rinses were performed each hour for 5 hours to establish the duration of the inhibiting effect. The results of these tests are shown in the chromatograms in figures 9 and 10. Fig. 9 shows the normal hydrogen sulfide production by the test subject in the morning after a rinse with cysteine, which is 10 mill AUC. After a rinse with the combination of 0.3% zinc acetate and 0.025% of chlorhexidine acetate and a further rinse with cysteine one hour later the HS value was only 32 000 (fig. 9a), after a further hour it was 500 000 (fig. 9b), then 270 000 (fig. 9c), 1.7 mill (fig. 9d) and 1.7 mill (fig. 9e). The combination thus reduced the hydrogen sulfide production in the mouth by cysteine with more than 80% five hours after a single rinse with the combination described above.

In a similar experiment with the combination of 0.3% zinc acetate and 0.025% cetylpyridinium chloride was tested. The normal value after the cysteine rinse was 11 mill AUC of hydrogen sulfide (fig. 10). After a rinse with the combination and a cysteine rinse one hour later the HS value was as low as 22 000 (fig. 10a). After two hours it was 67 000 (fig. 10b), after three hours 315 000 (fig. 10c), four hours 275 000 (fig. 10d) and five hours 47 000 (fig. 10e).

It can be concluded that the combinations of zinc acetate and the two tested antibacterials had a very strong and long lasting effect, and that chlorhexidine was not better than cetylpyridinium chloride in combination with zinc. It is probably safe to conclude that a mouthrinse of this type would inhibit oral malodor for eight hours or more under normal conditions.

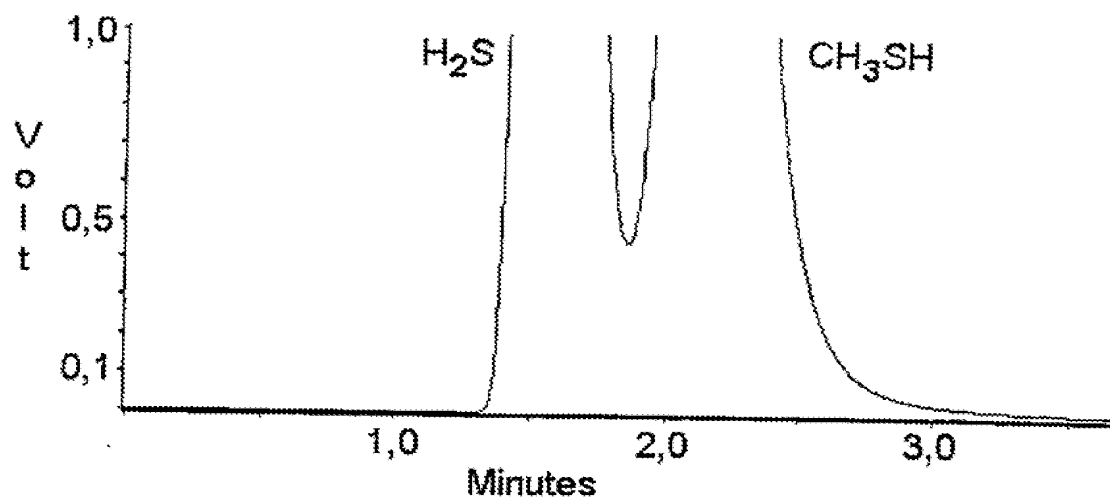
It was furthermore evident from additional experiments with the individual agents in the present experimental model, that the anti-VSC effect of the individual antibacterial agents was markedly inferior to the effect of the combinations. Synergistic effects of combinations of zinc acetate and the antibacterial agents were thus demonstrated also in the vivo model, which included hydrogen sulfide only (results not shown).

CLAIMS

1. Oral composition for inhibiting oral malodor, containing an antibacterial agent and a zinc compound, in the form of a mouthwash containing 0.005-
5 0.05% w/v of an antibacterial agent selected from bis-guanides and quaternary ammonium compounds, and 0.05-0.5% w/v of zinc acetate.
2. The oral composition of claim 1, wherein the mouthwash contains 0.01-0.025% w/v of an antibacterial agent and 0.1-0.3% w/v of zinc acetate.
- 10 3. The oral composition of any of claims 1 and 2, wherein the antibacterial agent is chlorhexidine or a salt thereof.
4. The oral composition of any of claims 1 and 2 wherein the antibacterial
15 agent is a quaternary ammonium compound selected from cetyl pyridinium chloride and benzalkonium chloride.

Sample ID: control

Acquired: Nov 20, 1998, 13:58:24



Results:

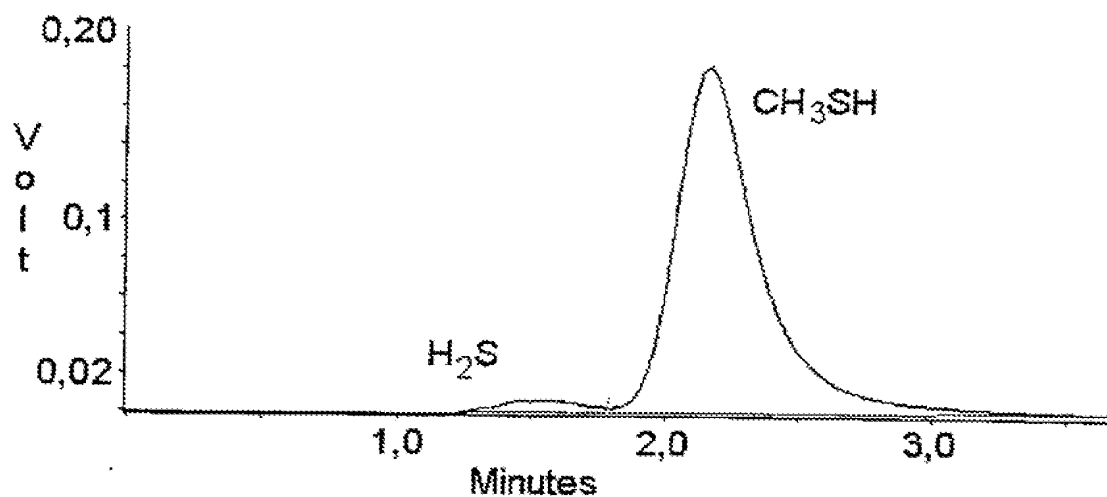
Peak	Area
H ₂ S	28302550
CH ₃ SH	41918978

Fig.1

2/20

Sample ID: saliva + 0,3% Zn acetate

Acquired: Nov 20, 1998, 14:12:06



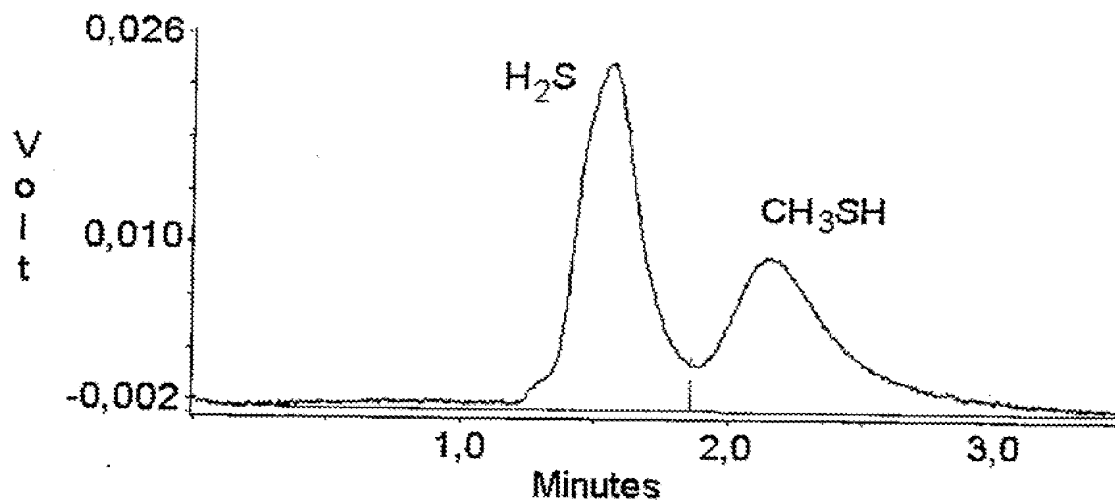
Results:

Peak	Area
H_2S	150256
CH_3SH	4028796

Fig.2

Sample ID: saliva + 0,025% CHX

Acquired: Nov 20, 1998, 14:21:00



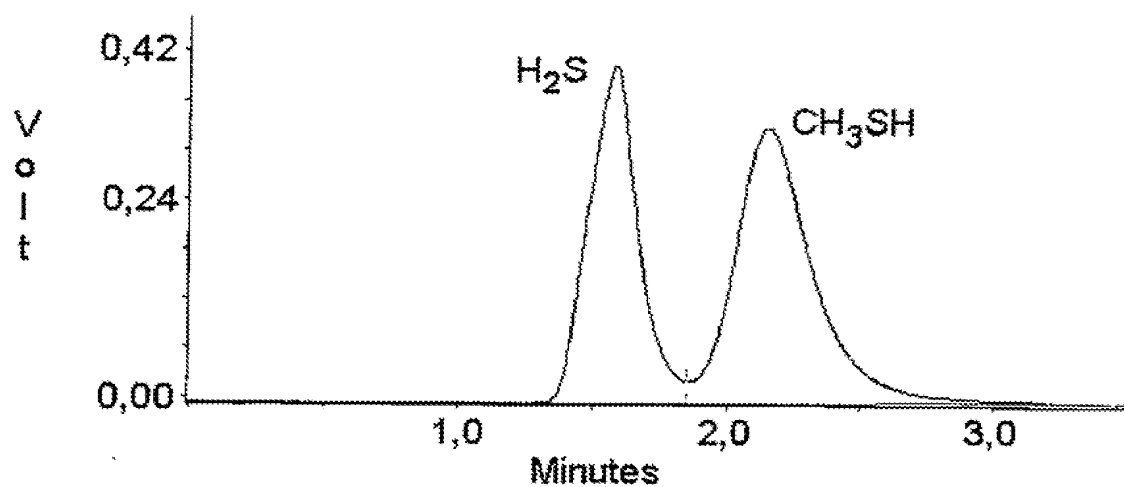
Results:

Peak	Area
H_2S	443348
CH_3SH	355001

Fig.3

4/20

Sample ID: saliva + 0,025% CPC
Acquired: Nov 20, 1998, 14:39:18



Results:

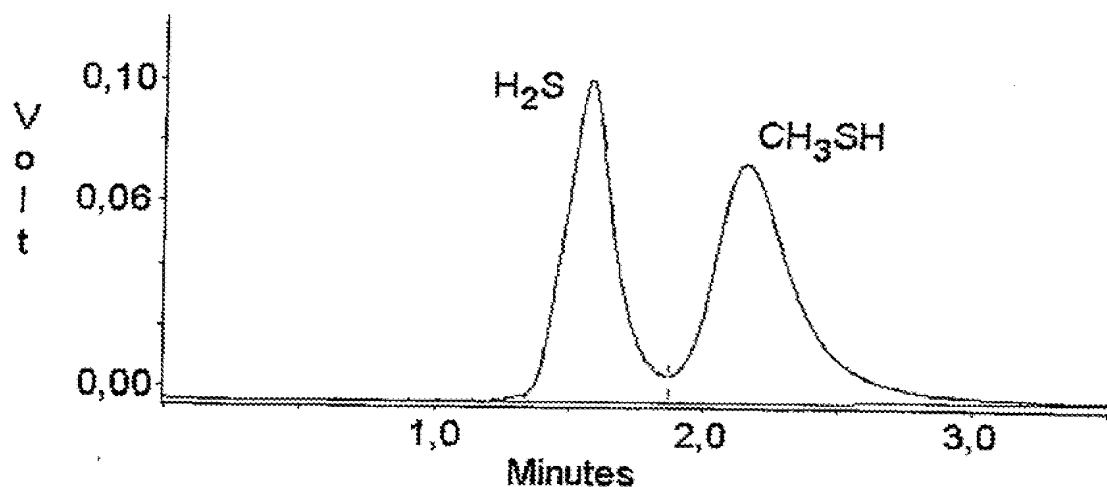
Peak	Area
H_2S	5264229
CH_3SH	6889886

Fig.4

5/20

Sample ID: saliva + 0,025% Banzlakonim Cl

Acquired: Nov 20, 1998, 14:29:40



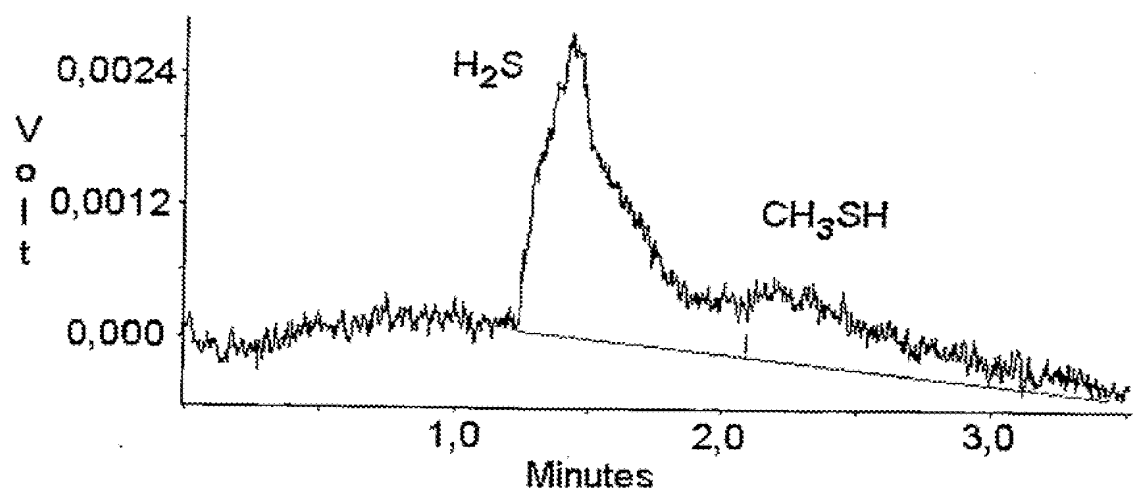
Results:

Peak	Area
H_2S	1402428
CH_3SH	1757520

Fig.5

Sample ID: saliva + 0,3% Zn-ac./ 0,025% CHX

Acquired: Nov 20, 1998, 15:02:53

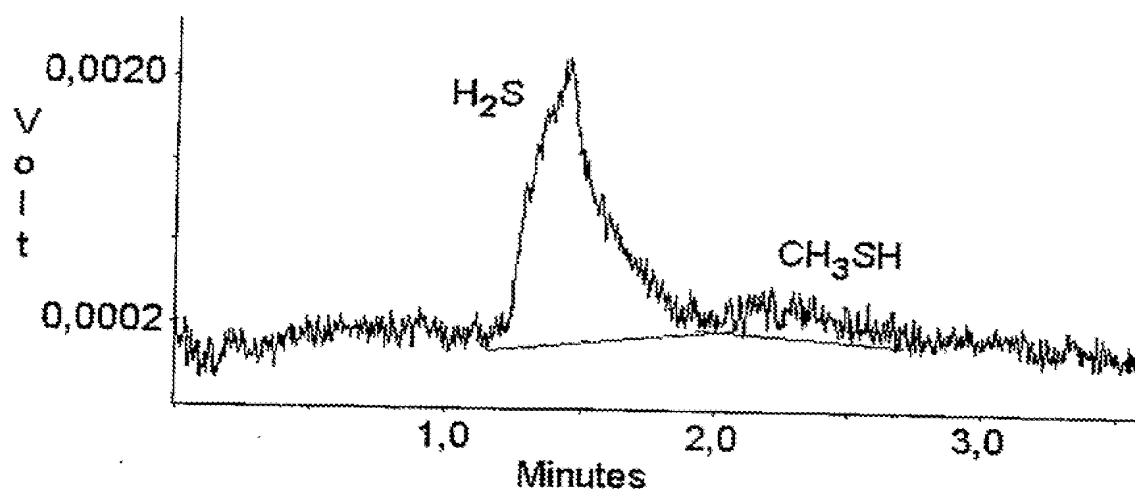


Results:

Peak	Area
H_2S	82516
CH_3SH	34430

Fig.6

Sample ID: saliva + 0,3% Zn-ac./ 0,025% Benzalkonium Cl
Acquired: Nov 20, 1998, 15:12:31



Results:

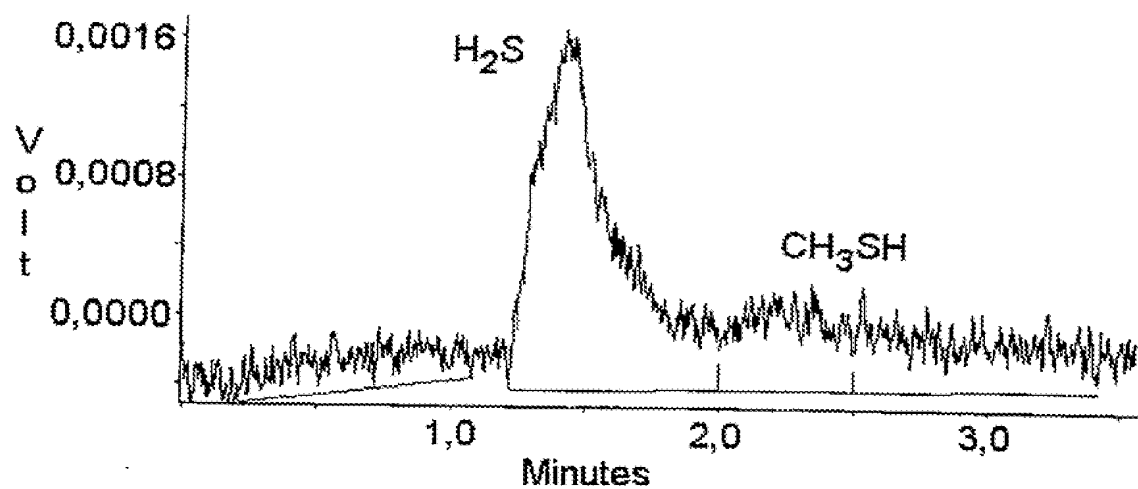
Peak	Area
H_2S	46971
CH_3SH	4063

Fig.7

8/20

Sample ID: saliva + 0,3% Zn-ac./ 0,025% CPC

Acquired: Nov 20, 1998, 15:17:18



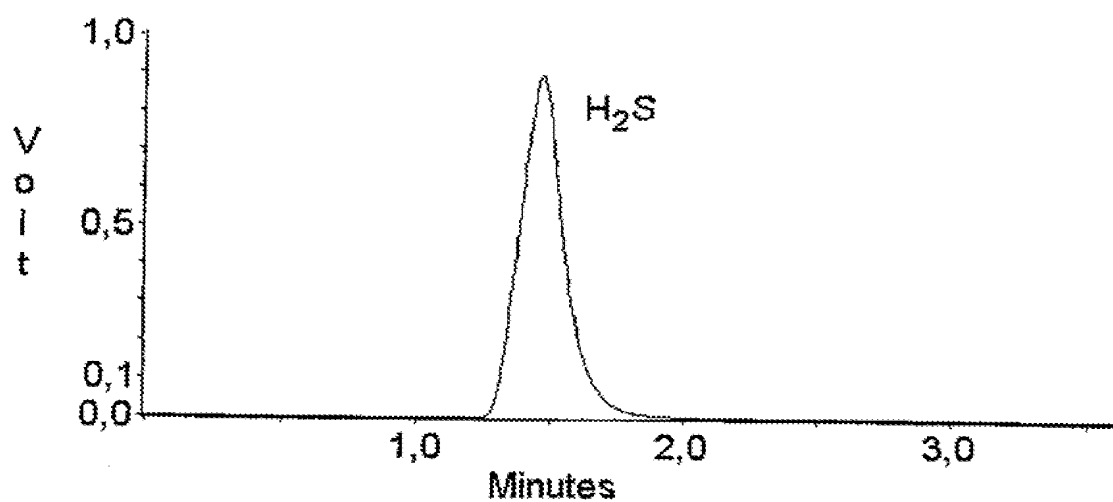
Results:

Peak	Area
H_2S	42749
CH_3SH	12245

Fig.8

Sample ID: cysteine

Acquired: Jan 18, 1999, 09:59:59



Results:

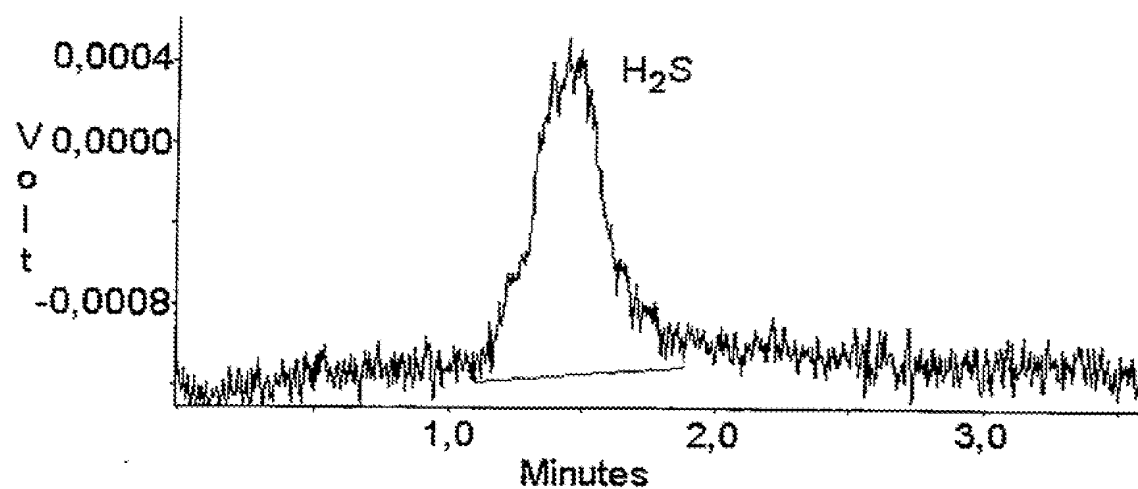
Peak	Area
H ₂ S	10777763

Fig.9

10/20

Sample ID: cysteine 1h. after CHX / Zn

Acquired: Jan 18, 1999, 11:05:56

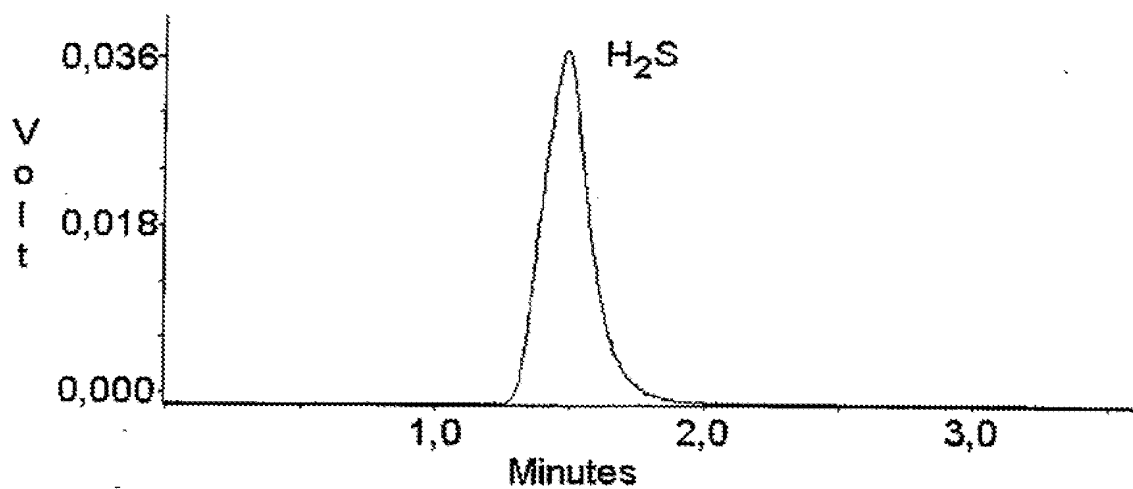


Results:

Peak	Area
H ₂ S	32230

Fig.9a

Sample ID: cysteine 2h. after CHX / Zn
Acquired: Jan 18, 1999, 12:00:28



Results:

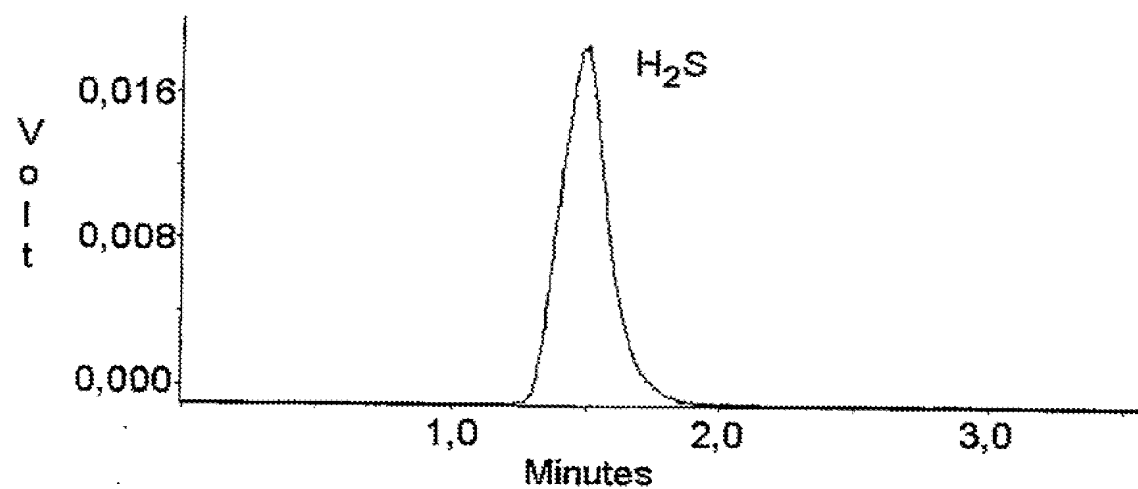
Peak	Area
H ₂ S	500089

Fig.9b

12/20

Sample ID: cysteine 3h. after CHX / Zn

Acquired: Jan 18, 1999, 13:01:44

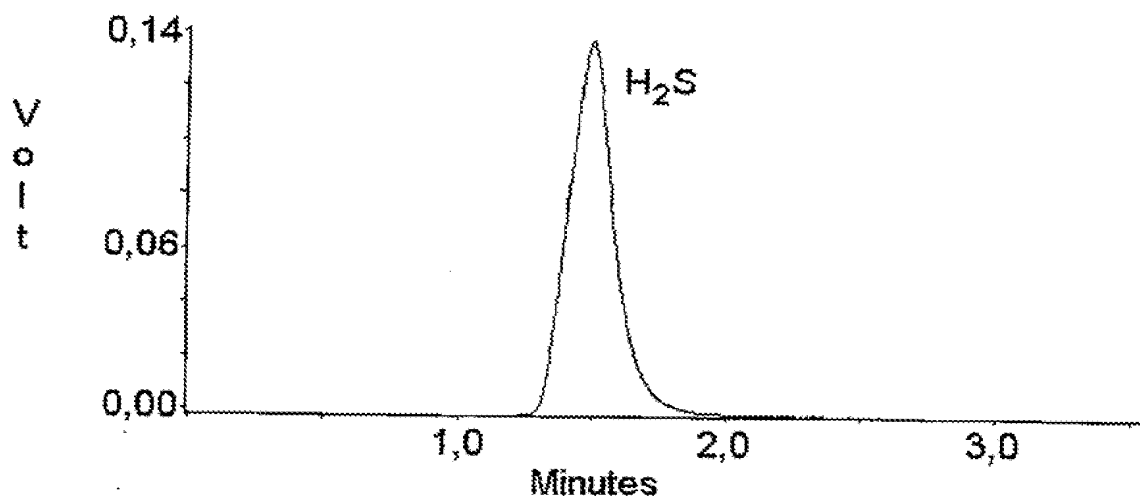


Results:

Peak	Area
H ₂ S	277783

Fig.9c

Sample ID: cysteine 4h. after CHX / Zn
Acquired: Jan 18, 1999, 14:05:12



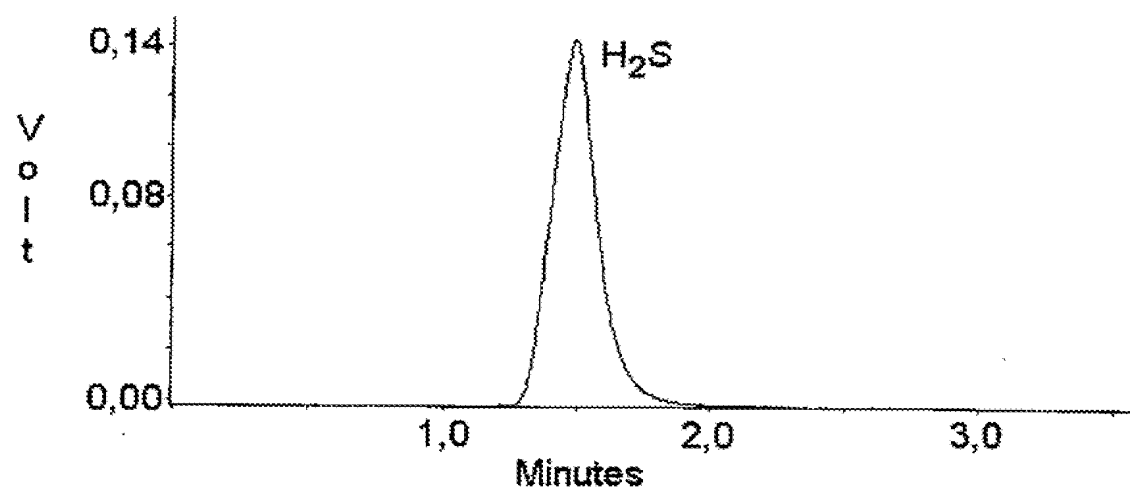
Results:

Peak	Area
H ₂ S	1713244

Fig.9d

Sample ID: cysteine 5h. after CHX / Zn

Acquired: Jan 18, 1999, 14:50:51



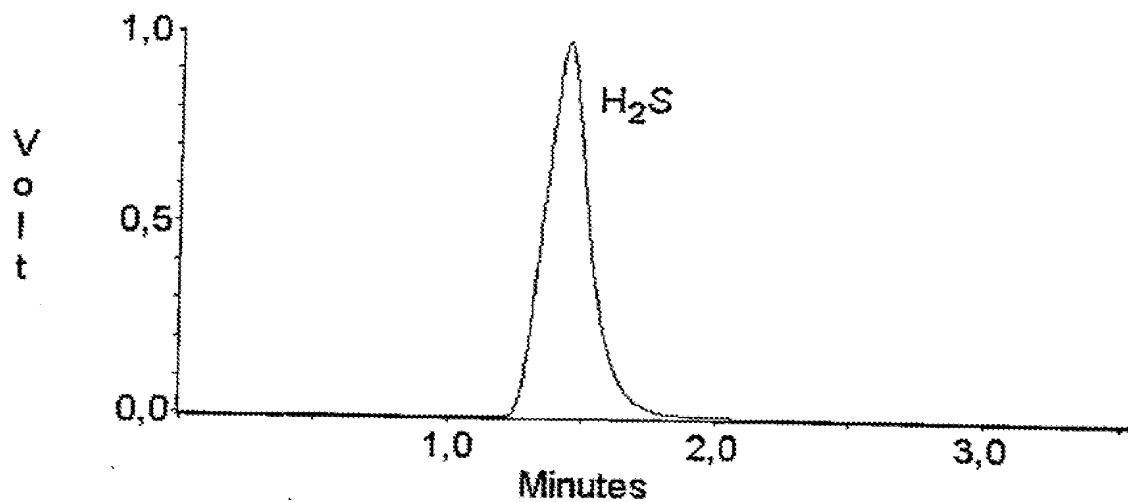
Results:

Peak	Area
H ₂ S	1769030

Fig.9e

Sample ID: cysteine

Acquired: Jan 19, 1999, 09:52:10



Results:

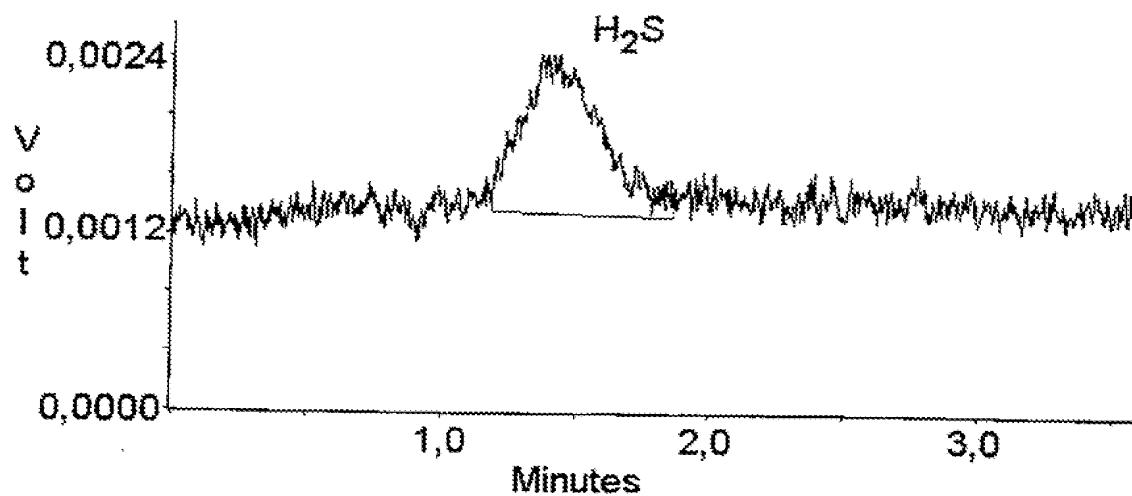
Peak	Area
H ₂ S	11646370

Fig.10

16/20

Sample ID: cysteine 1h. after CPC / Zn

Acquired: Jan 19, 1999, 11:04:09



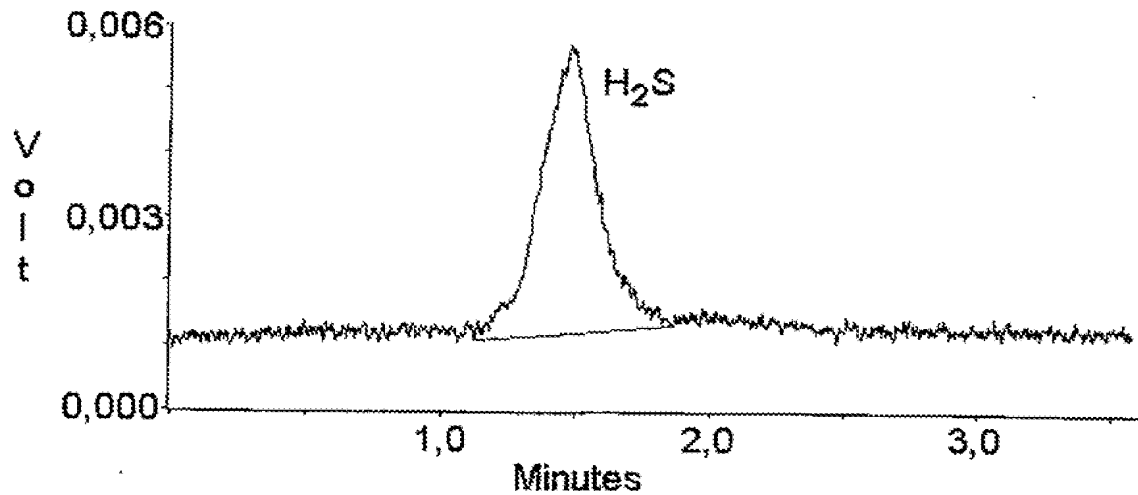
Results:

Peak	Area
H ₂ S	22209

Fig.10a

17/20

Sample ID: cysteine 2h. after CPC / Zn
Acquired: Jan 19, 1999, 12:01:07



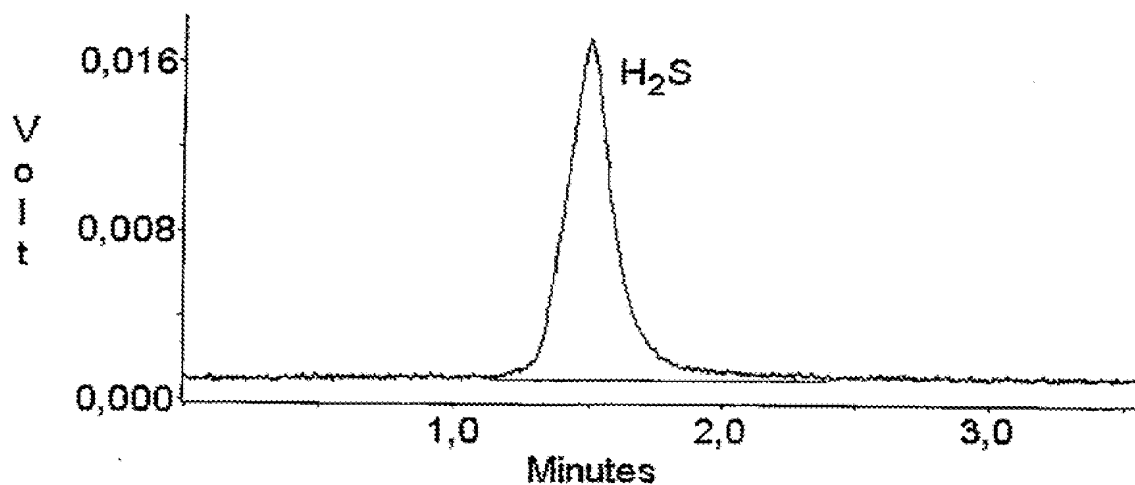
Results:

Peak	Area
H ₂ S	67676

Fig.10b

Sample ID: cysteine 3h. after CPC / Zn

Acquired: Jan 19, 1999, 12:56:33

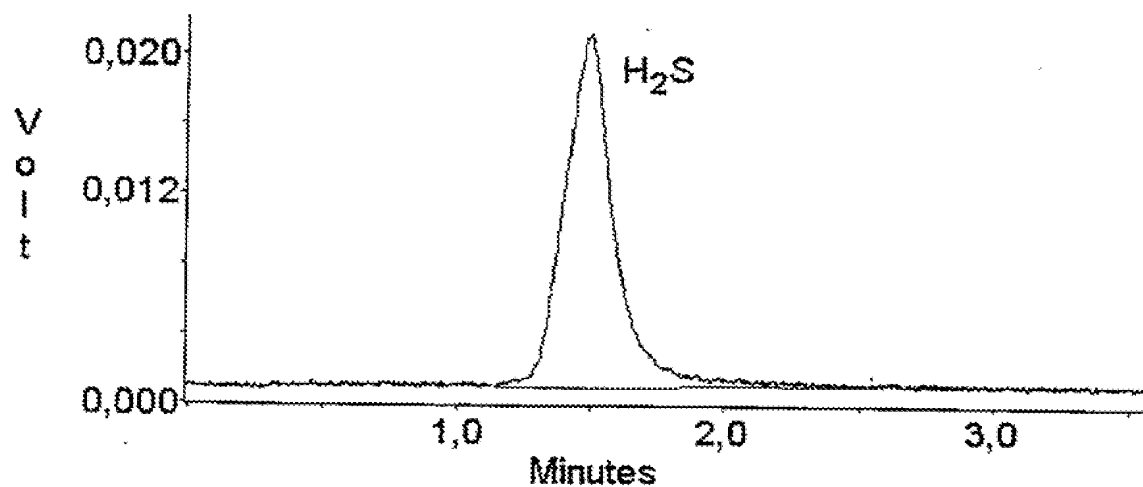


Results:

Peak	Area
H ₂ S	215678

Fig.10c

Sample ID: cysteine 4h. after CPC / Zn
Acquired: Jan 19, 1999, 13:55:40



Results:

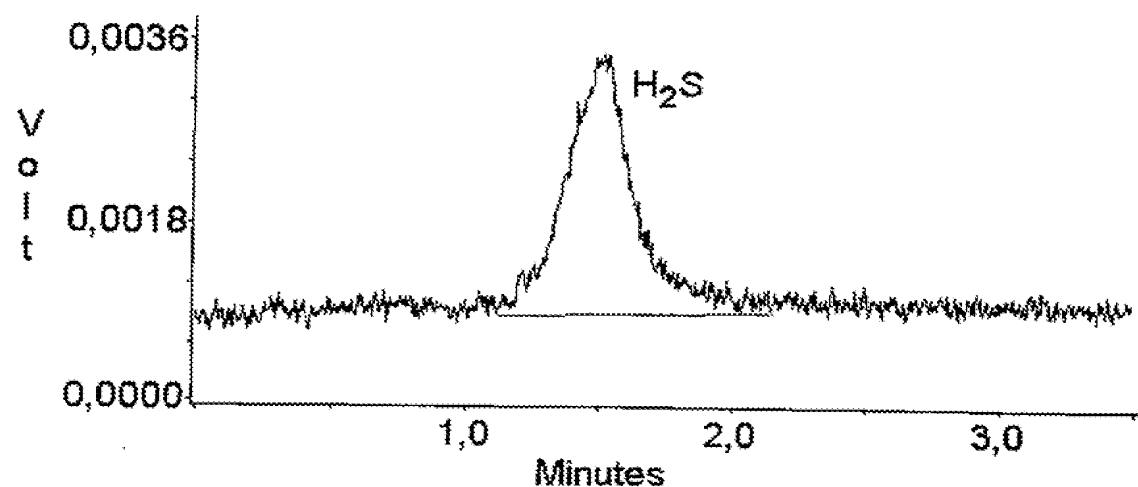
Peak	Area
H ₂ S	275812

Fig.10d

20/20

Sample ID: cysteine 5h. after CPC / Zn

Acquired: Jan 19, 1999, 15:12:20



Results:

Peak	Area
H ₂ S	47342

Fig.10e

INTERNATIONAL SEARCH REPORT

International application No.

PCT/NO 99/00346

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 7/16, A61K 7/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 3001575 A1 (BLENDAX-WERKE R. SCHNEIDER GMBH & CO.), 23 July 1981 (23.07.81) --	1-3
X	WO 9015592 A1 (SHANAHAN, PATRICK, JOHN), 27 December 1990 (27.12.90) --	1,2,4
A	EP 0181161 A2 (STAFFORD-MILLER CONTINENTAL), 14 May 1986 (14.05.86) --	1-3

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

14 April 2000

Date of mailing of the international search report

08-05-1999

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/NO 99/00346

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	scandinavian journal of dental research, Volume 99, No 4, 1991, Elin Giertsen et al, "Combined effects of Zn ²⁺ -chlorhexidine and Zn ²⁺ -cetylpyridinium chloride on caries incidence in partially desalivated rats" page 301 - page 309 --	1-4
A	J Dent Res, Volume 68, No 6, June 1989, E. Giertsen et al, "In vivo Effects of Zinc and Chlorhexidine on Dental Plaque Ureolysis and Glycolysis" page 1132 - page 1134 --	1-3
P,X	EP 0920857 A2 (DENTAID, S.A.), 9 June 1999 (09.06.99) ---	1-4
P,X	US 5948390 A (DENNIS G.A. ET AL), 7 Sept 1999 (07.09.99) -----	1,2,4

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.

PCT/NO 99/00346

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
DE	3001575	A1	23/07/81	NONE	
WO	9015592	A1	27/12/90	NONE	
EP	0181161	A2	14/05/86	NONE	
EP	0920857	A2	09/06/99	ES 1038174 U,Y ES 2132033 A	01/06/98 01/08/99
US	5948390	A	07/09/99	NONE	

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